Secreting Tumors of Chromaffin Tissue *

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FUNCTIONING chromaffin tumors are a rare but surgically curable cause of hypertension. Approximately 90 per cent develop within the medullary portion of the adrenal gland and are more commonly called pheochromocytomas. The remainder arise from the sympathetic ganglia or their ectopic remnants and are generally referred to as paragangliomas. The latter occasionally originate within the para-aortic bodies (organs of Zuckerkandl). These are paired structures located at the aortic bifurcation just distal to the origin of the inferior mesenteric artery. Although these bodies normally disappear by the second year of life, they may persist and hence predispose to subsequent tumor formation.[8] Regardless of location, chromaffin tissue is comprised of cells which are histologically similar and stain yellow with chromic acid. The designation *10 per cent tumor* has been applied to these neoplasms because 10 per cent are malignant, 10 per cent bilateral and, as already noted, 10 per cent are extra-adrenal.

Secreting paragangliomas of the organs of Zuckerkandl are most uncommon. Only 17 cases have been documented in the medical literature to date. Of these four have been surgically extirpated, with reversal of hypertension.[4, 11, 22, 25] It is the purpose of this discussion to present what the authors believe is the eighteenth case of a functioning paraganglioma, located at the organ of Zuckerkandl. It was surgically excised by one of the authors (P. A. R.) with reversal of the patient's hypertension. This case represents many if not most of the difficulties encountered in the diagnosis and management of secreting chromaffin tumors.

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Case Report

In February 1959, a 52-year-old Negro man was admitted to the U. S. Army Hospital, West Point, N. Y., for evaluation of an abdominal mass and for follow up care after the excision of a soft tissue lesion as an outpatient. The patient was a known hypertensive of eight years' duration. In 1954, while serving overseas, he suffered a cerebral hemorrhage and was left with a mild left-sided spastic paralysis. As a result of this he was retired from the active military service. Other pertinent data revealed the patient had neurofibromatosis (confirmed by biopsy specimen) and had undergone an uneventful hernioplasty the previous year. His medical records showed numerous and persistently elevated blood pressure determinations recorded by many different physicians. He had been evaluated in several hospitals and considered to have essential hypertension. On this admission his blood pressure was 180/110, and multiple determinations showed little variation. The abdominal mass was on the left and approximately 9.0×10 cm. Pertinent barium x-ray studies showed the mass to be retroperitoneal, but extrinsic to the gastro-intestinal or genito-urinary tract. He was operated upon with a tentative diagnosis of retroperitoneal neurofibroma. Exploration was performed through a long left paramedian incision. A $10 \times 9.0 \times 8.0$ cc. tumor was located in the region of Zuckerkandl's organ. During operative manipulation of the well-encapsulated tumor mass, there was a dramatic rise in blood pressure to 240/140, with the onset of auricular fibrillation. At this point the mass was recognized as a secreting paraganglioma. It was therefore gently manipulated in order to obtain immediate occlusion of its vascular pedicle. The neoplasm was found to be supplied by a large artery arising directly from the wall of the aorta and distal to the inferior

mesenteric artery. Following ligation of the blood supply, there was an equally abrupt drop in blood pressure to 90/50. Although blood loss had been minimal, the administration of four units of whole blood was effective in maintaining the systolic pressure at 100, with a normal pulse of good quality. The following day the patient's blood pressure had stabilized at 120/80, and his hemoglobin was 14.5 Gm. His subsequent blood pressure readings have levelled at a mean of 140/90. Final pathological study showed the tumor to be histologically similar to any other pheochromocytoma or paraganglioma.

Historical Aspects

The earliest autopsy report of an adrenal chromaffin tumor in a patient, who had symptoms consistent with a pheochromocytoma, was recorded in 1886.[10] The first successful surgical removal of a chromaffinoma, however, was performed by Mayo in 1927. Confronted with a 30-year-old woman, who was experiencing attacks of headache, pallor, nausea, and vomiting, and impressed by the concomitant marked increase in blood pressure, Mayo explored the patient in anticipation of finding some abnormality of the sympathetic nervous system. He was rewarded by finding a 6.0 $\times$ 4.0 cm. tumor in the left adrenal gland. The patient was subsequently relieved of her symptoms and remained normotensive. According to Ainley-Walker, 70 per cent of recorded pheochromocytomas have been found at autopsy [2] as an unexpected finding. The true incidence of secreting chromaffin tumors is consequently speculative because of failure to make the correct diagnosis. Graham had estimated that 600 to 800 new cases will arise annually in the nation.[16] One regional survey indicated that these neoplasms were responsible for 1.3 of every 100,000 hospital admissions.[21] By contrast, a physician in England recently reported two cases of pheochromocytoma within one year from among a practice of 2,800 patients.[30] Such statistics emphasize that these lesions are found more frequently when the clinician is aware of their existence.

Clinical Picture

While paroxysmal hypertension is the most significant manifestation of a chromaffinoma, hypertension is sustained in approximately a third of all cases. Tumor size and duration are obviously important to the development of sustained hypertension. Eventual impairment of cardiac and renal function is similar to that seen in other forms of hypertension and lethality derives from the same effects. These neoplasms show little predilection for either sex, but most frequently occur in the 20 to 50 age group. Children are not exempt, however, as Palmieri collected 68 cases in children under 14 years of age.[23] A seldom emphasized aspect of these tumors is that they are usually symptomatic. Blacklock found only 11.4 per cent of 141 cases reviewed were asymptomatic.[6] The clinical symptoms produced are directly attributable to overproduction of epinephrine or norepinephrine, or both, by the tumor cells. It has now been convincingly demonstrated that the adrenal medulla elaborates both substances while the chromaffin cells elsewhere produce only norepinephrine.[32] This is particularly helpful in differentiating tumors of adrenal or of extra-adrenal origin.

The typical *paroxysmal attack* is related to the sudden release of catecholamines. With a predominance of epinephrine, the cardiac output and rate increase, producing tachycardia, palpitations, and occasionally substernal distress. Although blood pressure rises, there will be a greater elevation of systolic than diastolic pressure. Other manifestations are headache, sweating, vertigo, nausea and vomiting, and visual disturbances in varying degrees. Norepinephrine acts more specifically as a vasoconstrictor of the peripheral vascular bed with resultant sharp rise in diastolic blood pressure and associated bradycardia. The frequency of attacks will vary from ten or more daily to but an isolated episode every few months. Paroxysms may last ten to 15

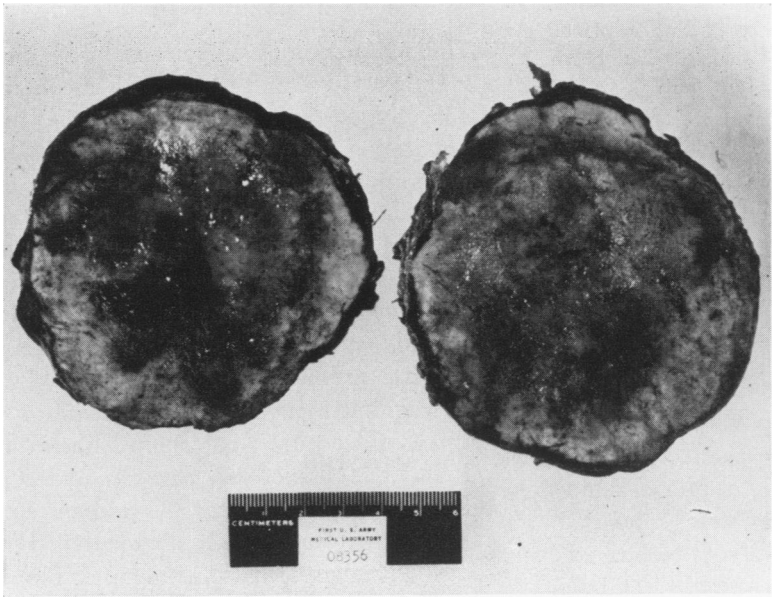

FIG. 1. Paraganglioma of the organ of Zuckerkandl. The gross specimen reveals a 9.0 × 9.0 × 8.0 cm. encapsulated tumor mass, cut in gross section. The cortex was golden yellow with a somewhat more reddish-yellow necrotic center.

minutes or longer or occasionally may be so transient as to last but seconds. Anxiety, emotional upset, changes in posture, and other occult stimuli have been known to precipitate an attack. In the case reported herein, the patient volunteered, in retrospect, that whenever he leaned forward to lace his shoes, he experienced a pounding headache. From the location of his tumor it is logical to assume that postural change produced compression of the neoplasm. When the act of urinating evokes an attack, one should consider the possibility of paraganglioma within the urinary bladder. Sivak recently collected 11 cases of functioning paragangliomas so located.[29] It is

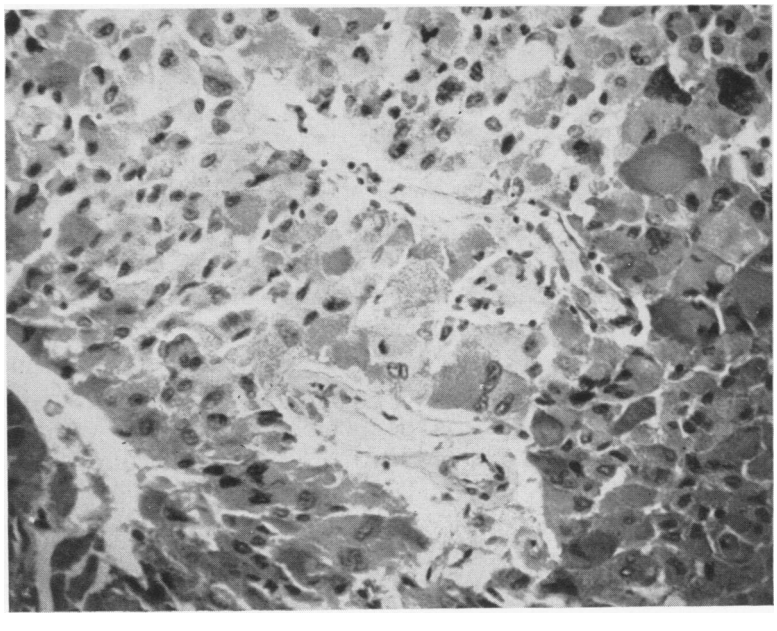

FIG. 2. Microscopic section of the tumor reveals sheets and nests of large polygonal cells with abundant granular cytoplasm and oval vesiculated nuclei. (H. & E. stain.)

also noteworthy that a documented case of pheochromocytoma with paroxysmal hypotension has occurred.[26] Such a situation is theoretically explained by the fact that small amounts of epinephrine may produce vasodilation without significantly altering cardiac output.

In the quiescent interval between attacks, there is generally increased circulating epinephrine sufficient to create and maintain a state of hypermetabolism. Elevated basal metabolic rate in association with other symptoms may lead to an erroneous diagnosis of thyrotoxicosis. In addition, the glycogenolytic effect of epinephrine frequently causes hyperglycemia with a demonstrably abnormal glucose tolerance curve. Elevated serum catecholamines also affect lipid metabolism by mobilizing fat from adipose tissue and causing its deposition in the myocardium,[19] liver, and renal tubules. The co-existence of chromaffin tumor and neurofibromatosis, as seen in this case report, is not unusual. Schlegel collected 45 cases from the literature in which both entities were present.[28] Other authors quote an incidence of from 5.0 to 30 per cent of neurofibromatosis in cases of chromaffinoma.[14, 18] The relationship between the two diseases is not readily apparent although both represent a neoplastic aberration of ectodermal tissue.

Helpful Diagnostic Aids

Pharmacologic tests used to support the diagnosis of chromaffinoma fall into three categories: 1) those tests employed to stimulate the tumor and provoke an attack of hypertension (provocative tests); 2) those intended to nullify the catecholamines and lower blood pressure by the administration of an adrenolytic agent (blocking tests); and 3) those which directly measure catecholamines and their by-products within serum or urine. Of the provocative tests, the histamine test of Roth and Kvale is the most widely used.[27] The most popular blocking test depends upon the adrenolytic effect of phentolamine (Regitine) to lower blood pressure.[12] It has wider applicability and a greater margin of safety, although false positives occur in patients who are uremic or who have been sedated with barbiturates or tranquilizers. Prior administration of antihypertensive agents may likewise give a false negative result. Measurement of serum and urinary catecholamines is more direct, more specific, and subject to less error.[15, 20] Elevated blood and urinary levels should be present even during the quiescent phase in patients subject to paroxysmal attacks. Armstrong [3] and Gitlow [13] described a simple screening test, which measures vanillylmandelic acid in urine by paper chromatography. Vanillylmandelic acid is a metabolic by-product of the degradation of catecholamines.

When chromaffinoma is reasonably suspected on the basis of the aforementioned clinical studies, it then becomes imperative to attempt to localize the tumor. The epinephrine secreting lesion limits location to either the right or left adrenal gland. Presacral retroperitoneal pneumotography has been advocated by many, while others prefer angiography. The combined advantages of both procedures have been demonstrated by Flint and Bartels.[9] They also reported no untoward effects in 400 instances where presacral air study was employed. Another approach is venous catheterization under fluoroscopic control. Blood samples taken from the area of the tumor have been shown to have increased elevations of catecholamines.[33]

Surgical Considerations

In general, an upper transverse abdominal incision is preferred. This permits exploration of both adrenals as well as the paravertebral sympathetic ganglia and region of the organs of Zuckerkandl. The right adrenal is readily exposed by downward and medial retraction of the hepatic flexure of the colon while simultaneously retracting the liver upward. By incising the

posterior peritoneum overlying the upper pole of the right kidney, the right adrenal is readily exposed. The left adrenal is more difficult, although it can be approached through the lesser sac. When the tumor is found, it should be gently manipulated and early ligation of its venous drainage performed. On the left side there is usually one large vein, which empties directly into the left renal vein. On the right side, however, multiple small veins drain the adrenal and empty directly into the vena cava.

Hypertensive crises are known to occur during tumor manipulation. Not infrequently patients harboring unsuspected chromaffin tumors develop acute hypertension during induction of anesthesia or during operation performed for unrelated disease.[31] The danger of such manipulation is attested to by the fact that it is accompanied by a 50 per cent mortality.[1] Administration of Regitine in doses of 2.5 mg. is the most effective means of controlling this reaction. Bartels and Catell [5] believe these hypertensive crises should be treated with the same urgency as in cardiac arrest. They recommend the following courses of action: 1) immediate discontinuance of the operation and further investigation on recovery; 2) in intra-abdominal operation, immediate exploration of the adrenals and the sympathetic chain areas, with removal of the tumor if found; and 3) an adrenolytic drug to control hypertension followed by continuance of the initial operation, and postoperative investigative studies to confirm the presence of a chromaffin tumor (the response of blood pressure to the adrenolytic drug providing additional evidence).

Development of shock following resection of the tumor and coincident with ligation of its venous return is not uncommon. For many years this phenomenon was attributed to myocardial strain and left ventricular failure. It has been more recently shown, however, that the mechanism is true peripheral vascular collapse or vasodilatation. Peripheral arteries and arterioles essentially become adjusted to high circulating levels of norepinephrine. When excess production of these hormones suddenly ceases, the vessels are unable to maintain normal tonic contraction, and vasodilatation follows. Administration of large volumes of blood frequently is insufficient to restore blood pressure. However, prompt use of norepinephrine, which can be titrated by intravenous drip (4.0 mg. in 1,000 cc. of 5.0% glucose in water) is usually adequate until stability of the circulation returns and norepinephrine therapy can be discontinued.[17] Additionally, it should be mentioned that if preoperative localization of the tumor is not possible and abdominal exploration fails to disclose it, consideration must be given to more remote possibilities. Chromaffinomas have been reported as occurring both intracranially [7] and in the thoracic cavity.[24]

Summary

Functioning tumors of chromaffin tissue are more common than originally thought, as evidenced by the attention they are presently receiving in medical literature. As a surgically curable cause of hypertension, the tumors must be actively sought if early diagnosis and corrective operation is to be performed. An unusual case of secreting paraganglioma occurring at the organ of Zuckerkandl is herein reported. Current theories and knowledge regarding clinical symptoms and manifestations produced by excess production of catecholamines have been briefly discussed together with the interesting background history.

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